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Sex hormonal modulation of interhemispheric transfer time.

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Abstract

It is still a matter of debate whether functional cerebral asymmetries (FCA) of many cognitive processes are more pronounced in men than in women. Some evidence suggests that the apparent reduction in women's FCA is a result of the fluctuating levels of gonadal steroid hormones over the course of the menstrual cycle, making their FCA less static than for men. The degree of lateralization has been suggested to depend on interhemispheric communication that may be modulated by gonadal steroid hormones. Here, we employed visual-evoked EEG potentials to obtain a direct measure of interhemispheric communication during different phases of the menstrual cycle. The interhemispheric transfer time (IHTT) was estimated from the interhemispheric latency difference of the N170 component of the visual-evoked potential from either left or right visual field presentation. Nineteen right-handed women with regular menstrual cycles were tested twice, once during the menstrual phase, when progesterone and estradiol levels are low, and once during the luteal phase when progesterone and estradiol levels are high. Plasma steroid levels were determined by blood-based immunoassay at each session. It was found that IHTT, in particular from right-to-left, was generally longer during the luteal phase relative to the menstrual phase. This effect occurred as a consequence of a slowed absolute N170 latency of the indirect pathway (i.e. left hemispheric response after LVF stimulation) and, in particular, a shortened latency of the direct pathway (i.e. right hemispheric response after LVF stimulation) during the luteal phase. These results show that cycle-related effects are not restricted to modulation of processes between hemispheres but also apply to cortical interactions, especially within the right hemisphere. The findings support the view that plastic changes in the female brain occur during relatively short-term periods across the menstrual cycle.

Keywords

Corpus callosum, estradiol, gender, hemispheric asymmetry, interhemispheric transfer time, menstrual cycle, sex

Introduction

It is well established that the cerebral hemispheres are specialized for particular cognitive, emotional and motor processes. Language functions, for example, are predominantly carried out in the left cerebral hemisphere, whereas spatial and emotional processing is predominantly performed in the right (Hugdahl & Westerhausen, 2010). It is also generally accepted that these functional cerebral asymmetries (FCA) are more pronounced in men than women (e.g. McGlone, 1980; Shaywitz et al., 1995). However, sex differences in FCAs are not always found (e.g. Sommer, Aleman, Bouma, & Kahn, 2004), partly because sex hormonal factors have been largely ignored (Hausmann, 2010; Hausmann & Bayer, 2010). In fact, considerable evidence has accumulated that suggests that FCAs in women are modulated by fluctuations in gonadal steroid hormones across the menstrual cycle (e.g. Bibawi, Cherry, & Hellige, 1995; Hausmann, 2005; Hausmann, Becker, Gather, & Güntürkün, 2002; Hausmann & Güntürkün, 2000; Heister, Landis, Regard, & Schroeder-Heister, 1989; McCourt, Mark, Radonovich, Willison, & Freeman, 1997; Mead & Hampson, 1997; Rode, Wagner, & Güntürkün, 1995; Sanders & Wenmoth, 1998; Weis, Hausmann, Stoffers, & Sturm, 2008; Weis, Hausmann, Stoffers, Vohn, Kellermann, & Sturm, 2011). In addition, FCAs change as a consequence of hormone therapy in postmenopausal women (Bayer & Erdmann, 2008; Bayer & Hausmann, 2009a). It is currently unclear which hemisphere is predominately sensitive to the influence of sex hormones. Some studies suggest the left hemisphere is particularly affected by sex hormones (e.g., Bibawi et al., 1995;

Hampson, 1990a; 1990b), while others suggest it is the right (e.g., Bayer & Hausmann, 2009a; Sanders & Wenmoth, 1998).

Hausmann and Güntürkün have proposed that FCAs are affected via mechanisms that alter processing in both hemispheres. They proposed that it is the *interaction* between hemispheres that is affected by fluctuations of sex hormones across the menstrual cycle (Hausmann & Güntürkün, 2000). Specifically, it was suggested that a cycle-dependent increase in progesterone concentration during the luteal phase of the menstrual cycle decreases glutamatergic, and increases GABA receptor activation. These effects lead, via a decrease of transcallosal neuronal activation, to hemispheric decoupling, which reduces FCAs. This view holds that the principal role of callosal communication is the inhibition of the non-dominant hemisphere by the dominant hemisphere. The reduction of callosal communication would reduce the inhibition of neurons in the non-dominant hemisphere, this in turn would result in an increase in bilateral activation resulting in a reduction in FCA (e.g. Cook, 1984; Regard, Cook, Wieser, & Landis, 1994). Hausmann and Güntürkün (2000) argued that this occurs in spite of cortico-cortical connections being mainly excitatory, as the main and longer lasting effect of callosal activation appears to be inhibitory (Innocenti, 1980; 1986). This is argued to be because many callosal fibers terminate on pyramidal neurons that then activate GABAergic interneurons (Toyama & Matsunami, 1976; Toyama, Tokashiki, & Matsunami, 1969). It is also likely that many excitatory transcallosal fibres terminate directly on inhibitory interneurons (Conti & Manzoni, 1994). Either way, these activated inhibitory neurons could then induce a widespread inhibition in homotopic regions of the contralateral hemisphere (Conti & Manzoni, 1994). Consistent with this view are the findings from an fMRI study of word matching (Weis et al., 2008) that found both cycle-related changes in error rates and response times, and cycle-related fluctuations in neural activity. Although no general significant cycle-related (menstrual versus follicular phase) difference in activation of

the left inferior frontal gyrus (i.e. Broca's area) was found, a connectivity analysis revealed that the inhibitory influence of the dominant on the non-dominant hemisphere fluctuated across the menstrual cycle. Specifically, it was shown that the inhibitory influence of left-hemispheric language areas on homotopic areas of the right hemisphere was strongest during menses, resulting in a pronounced lateralization. In contrast, during the follicular phase, inhibition (and thus FCA) was reduced due to increased estradiol levels. In contrast, interhemispheric inhibition remained stable in men over a period of two weeks.

The original model by Hausmann and Güntürkün (2000) has been revised recently (Hausmann & Bayer, 2010) to take into account some new findings. The revised *Hypothesis of Sex Hormone-Modulated Cortical Interaction* differs from the original model in three main aspects. First, it is suggested that interhemispheric decoupling is not solely progesterone dependent, but may also be influenced by estradiol (e.g. Hausmann, 2005; Holländer, Hausmann, Hamm, & Corballis, 2005; Weis et al., 2008), although the neural mechanisms are not fully clear. Second, the effects of gonadal steroid hormones are not restricted to interhemispheric inhibition, which has been assumed to be the key mechanism in generating hemispheric asymmetries. Sex hormones also affect other aspects of interhemispheric interaction (e.g. interhemispheric integration), and thus their influence is not limited to the manifestation of hemispheric asymmetries (Bayer & Hausmann, 2009b; Bayer, Kessler, Güntürkün, & Hausmann, 2008). Third, sex hormonal effects are not restricted to the modulation of interhemispheric crosstalk but can also apply to cortical interactions within hemispheres. In fact, visual half-field studies in postmenopausal women using hormone therapy revealed that it is the right hemispheric performance in particular that is modulated by (synthetic) gonadal steroid hormones (Bayer & Erdmann, 2008; Bayer & Hausmann, 2009b).

A TMS study (Hausmann, Tegenthoff, Sängler, Janssen, Güntürkün, & Schwenkreis,

2006) has addressed the activating effects of progesterone and estradiol on interhemispheric inhibition on a neural level. TMS applied to the primary motor cortex evokes a suppression of tonic voluntary muscle activity contralateral *and* ipsilateral to the stimulation (Ferber, Priori, Rothwell, Day, Colebatch, & Marsden, 1992; Wasserman, Fuhr, Cohen, & Hallett, 1991). The ipsilateral suppression, called ipsilateral silent period, is probably mediated cortically by excitatory transcallosal fibres targeting inhibitory interneurons. Therefore, the ipsilateral silent period might reflect the functional integrity of the connection between homotopic areas of left and right primary motor cortices (e.g. Ferbert et al., 1992) and so provide an estimate of interhemispheric inhibition. It has been shown that the ipsilateral silent period fluctuates across the menstrual cycle, with the largest suppression/inhibition during the luteal phase (high levels of estradiol and progesterone) compared to the follicular phase (high estradiol levels). These results are consistent with the predictions of the revised model, and strongly suggest that both estradiol and progesterone can independently modulate interhemispheric processes across the menstrual cycle. It should be noted, however, that using muscle activity as the dependent variable is a rather indirect measure of interhemispheric (de)coupling. It is quite possible that gonadal steroid hormones have effects at a number of loci other than at the targets of transcallosal neurons, there may be other explanations for these data.

A much more direct measure of interhemispheric (de)coupling involves recording the hemispheric latency differences between visual potentials (e.g. the N170 component) evoked by briefly stimulating either the right or left visual fields. The IHTT can be derived by calculating the difference between the latency of the evoked potential in the directly stimulated contralateral hemisphere and that of the evoked potential in the ipsilateral hemisphere, which is believed to be generated by the transfer of information via the corpus callosum (Saron & Davidson, 1989). Previous work employing visual-evoked potentials to measure IHTT, revealed a directional asymmetry in conduction velocities between

hemispheres (e.g. Barnett, Corballis, & Kirk, 2005; Barnett & Kirk, 2005; Brown, Larson, & Jeeves, 1994; Iwabuchi & Kirk, 2009; Moes, Brown, & Minnema, 2007; Nowicka & Fersten, 2001; Patston, Kirk, Rolfe, Corballis, & Tippet, 2007; Rolfe, Kirk, & Waldie, 2007; Saron & Davidson, 1989; see also Marzi, 2010, and Nowicka & Tacikowski, 2011, for reviews). The transfer of neural information from the right hemisphere to the left is faster than transfer from the left hemisphere to the right. At least this is the case for right-handed males. Left-handers (Iwabuchi & Kirk, 2009), musicians (Patston et al., 2007), those with a variety of neurological disorders (Barnett et al., 2005; Barnett & Kirk, 2005; Rolfe et al., 2007), and, of particular relevance here, females (Moes et al., 2007; Norwicka & Fersten, 2001) differ from this pattern and show more symmetrical IHTTs. This fits with numerous reports of less FCA in these groups (e.g. Bourne, 2005; Galaburda, Lemay, Kemper, & Geschwind, 1978; Hausmann, Behrendt-Korbitz, Kautz, Lamm, Radelt, & Güntürkün, 1998; McGlone, 1980; Shaywitz, et. al., 1995; Witelson, 1976).

The aim of the present study is to expand on these previous reports of a sex difference in the degree of asymmetry of directional IHTTs and investigate whether IHTT differs across the menstrual cycle as the levels of estradiol and progesterone fluctuate. This is the first electrophysiological study on IHTT that measured participants' serum hormone levels. It is expected that, in line with the (revised) Hausmann and Güntürkün model, IHTT will generally lengthen during the luteal phase. In addition, it is predicted that the degree of asymmetry of directional IHTTs will decrease in the luteal phase. Given that IHTT is a composite measure of direct and indirect N170 latencies, cycle-related modulations of both pathways will also be analysed separately. This will allow us to test the specific hypothesis that it is especially the latency of the indirect right-to-left pathway that is affected during the luteal phase.

Methods

Subjects

Twenty-four normally cycling women with a mean age of 26.96 years (SD = 6.19; range: 19-42 years) were investigated. All women were right-handed, as determined with the Edinburgh-Inventory (Oldfield, 1971). The asymmetry-index (LQ) provided by this test is calculated as $[(R-L)/(R+L)] \times 100$, resulting in values between -100 and +100. This range describes the continuum from extreme sinistrality to extreme dextrality. The mean LQ of female participants was 80.23 (SD = 18.02; range: 47.0 to 100) and the reading direction of all participants was left-to-right. Women who had used oral contraceptives or any other medication affecting the central nervous system during the last six months before testing were excluded. All participants had normal or corrected-to-normal visual acuity and were naive to the study's hypotheses. They were recruited by announcements, and were paid for their participation. Female participants also took part in other experiments investigating the hormone effects on cognitive abilities and the functional cerebral organisation.

Procedure

The procedure has been adapted from Barnett, Corballis and Kirk (2005) and is similar to previous studies (e.g. Nowicka, Grabowska & Fersten, 2001). Participants were seated in front of a SVGA monitor (640 x 480 pixel resolution) at a distance of 57 cm in a quiet, electrically shielded Faraday chamber during the experiment. They were presented with a total of 260 stimuli: 120 left visual field (LVF), 120 right visual field (RVF), and 20 catch trials of no stimuli, which were broken into four blocks that were in a counterbalanced order for the responding hand. The stimuli were circular checkerboards with a diameter of three degrees of visual angle and squares of 6 x 6 pixels, producing 3 checks per degree at 57 cm viewing distance. The stimuli were positioned six degrees horizontally from the central

fixation cross in the LVF or RVF. Following presentation of the fixation cross for 1000 ms, a stimulus was presented for 100 ms, with a randomized and varied inter-stimulus interval of 550, 750 or 950 ms. Participants were instructed to respond immediately after detecting a stimulus in any position by pressing the space bar on the keyboard. A brief practice session was provided prior to electroencephalogram (EEG) recording.

EEG Acquisition and Analysis

EEG activity was recorded continuously on an Electro Geodesics Inc. 128-channel Ag/AgCl electrode net (Electrical Geodesics Inc., Eugene, OR, USA) at a sampling rate of 1000-Hz. The impedances of electrodes ranged between 35 and 40 k Ω . A common vertex (Cz) served as the reference, which was later re-referenced to the common average reference. Recordings contaminated by eye blinks (rejection criterion of 70 μ V in eye channels) were rejected and automatic eye-movement correction was conducted on the remaining segments (Jervis et al., 1985). In line with previous studies (e.g. Barnett, Corballis & Kirk, 2005; Nowicka, Grabowska & Fersten, 2001), recordings of each participant were segmented into epochs with a pre-stimulus baseline of 100 ms and a post-stimulus period of 500 ms, which were then averaged for each visual half-field (VHF) condition (LVF or RVF). The recordings were bandpass filtered using a bi-directional three pole Butterworth filter between 0.1 and 30 Hz (Alarcon, Guy, & Binnie, 2000). The N170 component was determined as the greatest negative peak between 140 and 250 ms following stimulus onset and were acquired separately for each participant for electrode clusters in and surrounding P7 and P8 parietal sites (according to the international 10-20 system). The parietal sites were selected because “IHTTs from parietal electrodes are sensitive to stimulus properties and, thus, are likely to reflect callosal transfer of important aspects of visual stimulus information” (Brown & Jeeves, 1993, p. 1270). Moreover, parietal sites showed the most pronounced N170

component bilaterally. The present study focused on interhemispheric N170 latency difference as the measure of IHTT, rather than that for P100 for example, as the N170 difference has been suggested to be the most reliable IHTT measure (Brown & Jeeves, 1993). Channels showing excessive alpha activity were excluded. IHTTs were calculated by subtracting the N170 latency of the mean ERP from the electrode cluster contralateral to the stimulus from the N170 latency of the mean ERP from the electrode cluster ipsilateral to the stimulus (see Figure 1). The amplitude of the N170 was calculated as the voltage deflection at the N170 peak relative to the baselined waveform (baselined from -100 ms to 0 ms). IHTTs were analysed using a two-way, within-subjects ANOVA, with transfer direction (right-to-left, left-to-right) and menstrual phase (menstrual, luteal) as the within-subjects factors. In addition, N170 latencies were analyzed using a 2 x 2 x 2 repeated measures Analysis of Variance (ANOVA) with menstrual phase (menstrual, luteal), hemisphere (left, right) and VHF (LVF, RVF) as within-subject factors. All statistical analyses were conducted on SPSS 17.0 for Windows and used an alpha level of .05. All post hoc t-tests were alpha-adjusted (Bonferroni).

Hormone assays

Prior to the experimental session, women were informed about the general procedure and data were collected about their individual menstrual cycles. All women agreed to inform us of the first day of their next cycle, in order to plan the dates for the experimental sessions. The normally cycling women were tested twice, once during the menstrual phase (cycle day 1 - 5) and once during the luteal phase (cycle day 21 – 22), to yield the largest differences in estradiol and progesterone levels. To control for potential repeated-measures effects, half of the female group was first tested during the luteal phase, and later tested during the menstrual phase and vice versa. Directly after every session a blood sample was collected. Serum

estradiol and progesterone levels for each cycle phase were determined with Chemiluminescent Microparticle Immunoassay (CMIA) by an independent professional medical laboratory, with commercially available CMIA kits.

Mood

Since cycle-dependent fluctuations in mood can affect interhemispheric processes (Compton & Mintzer, 2001), the State-Trait-Cheerfulness-Inventory (STCI-S18; Ruch, Köhler, & van Thriel, 1996; 1997) was applied during each test session. The STCI-S18 is an instrument measuring the three concepts of cheerfulness, seriousness, and bad mood. The concept of ‘cheerfulness’ represents positive affect, such that subjects with a high score describe themselves (e.g. as being “in good spirits” or “in a mirthful mood”). The concept of ‘seriousness’ is understood as the readiness to perceive, act, or communicate seriously (e.g. “I’m prepared to do a task in earnest”). The concept of ‘bad mood’ is defined by the two elements of sadness/melancholy and ill humor (e.g., “I am in a bad mood”, “I am sad”, “I am in a grumpy mood”). Each concept included 6 items and the response was given on a 4-point rating-scale (strongly disagree = 1, moderately disagree = 2, moderately agree = 3, and strongly agree = 4).

Results

Hormone assays

Nineteen normally cycling women completed two test sessions. Five women were excluded because they completed only one session and one woman was excluded because her progesterone levels were close to the detection limit in both sessions, suggesting an absence of ovulation in this participant. The mean level of serum progesterone in the remaining 19 women was 1.0 (SD = 0.5) nmol/L in the menstrual phase and 32.0 (SD = 16.0) nmol/L in the

luteal phase. The mean level of serum estradiol of the 19 women was 181.9 (SD = 41.1) pmol/L in the menstrual phase and 564.4 (SEM = 188.0) pmol/L in the luteal phase. Paired *t*-tests revealed significant cycle-phase differences in both the mean serum progesterone, $t(18) = 8.34$, $p < 0.001$, and the mean serum estradiol levels, $t(18) = 8.73$, $p < 0.001$.

Mood

Paired *t*-tests revealed no significant differences in mood between menstrual and luteal cycle phase in cheerfulness (menstrual: 2.64 ± 0.77 , luteal: 2.77 ± 0.97 , $t(18) = 0.42$, n.s.), seriousness (menstrual: 2.87 ± 0.39 , luteal: 2.71 ± 0.47 , $t(18) = 1.43$, n.s.), and bad mood (menstrual: 1.67 ± 0.76 , luteal: 1.72 ± 0.75 , $t(18) = 0.28$, n.s.).

IHTT

The latency differences between the N170 recorded in the hemisphere ipsilateral and contralateral to the field of stimulation were the basis for the cycle-phase dependent analysis of IHTT in both directions: from the left hemisphere to the right and from the right hemisphere to the left (see Figure 1). A menstrual phase (menstrual, luteal) by transfer direction (left-to-right, right-to-left) repeated measures ANOVA was conducted on IHTT. The analysis revealed a significant main effect of cycle phase ($F(1, 18) = 22.42$, $p < .001$, $\eta_p^2 = .56$), indicating longer IHTT in the luteal phase, and a cycle phase by transfer direction interaction, $F(1, 18) = 9.50$, $p = .006$, $\eta_p^2 = .36$. The main effect of transfer direction was not significant, $F(1, 18) = 0.02$, $p = .89$, $\eta_p^2 = .001$. As shown in Figure 2, right-to-left IHTT was significantly shorter during the menstrual phase (Mean \pm SD) ($11.16 \text{ ms} \pm 7.25$) relative to the luteal phase ($23.68 \text{ ms} \pm 10.71$; $t(18) = 5.12$, $p < .001$), whereas this difference only approached significance for left-to-right transfer (menstrual phase: 14.74 ± 6.54 , luteal phase: 19.37 ± 10.85 , $t(18) = 2.36$, $p = .03$, not significant after Bonferroni correction). Post hoc *t*-

tests also showed that the transfer time did not differ based upon direction during either the menstrual phase, $t(18) = 1.79$, $p=.09$, or the luteal phase, $t(18) = 1.19$, $p=.25$.

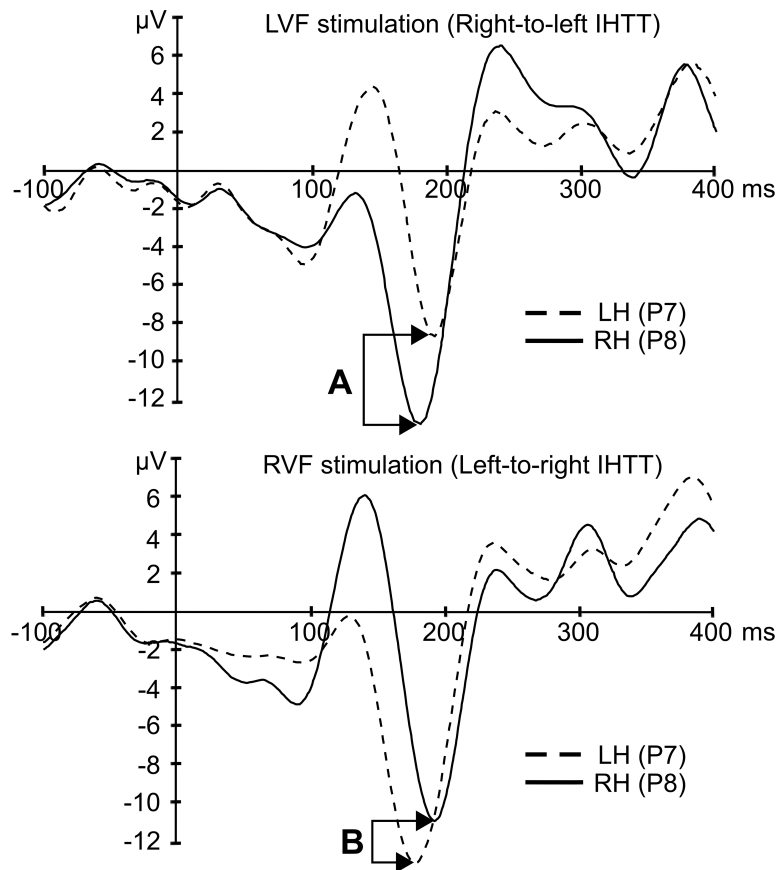


Figure 1. Event-related potential (ERP) waves for left visual half-field (LVF, right-to-left IHTT (“A”), top pannel), and right visual half-field (RVF, left-to-right IHTT (“B”), bottom panel) presentations during the menstrual cycle. Left and right hemisphere electrodes (parietal leads P7 and P8, respectively) are shown for LVF and RVF presentation respectively. Right-to-left IHTT calculated as latency difference at N170 between right and left hemisphere electrodes after LVF presentation (“A”, top panel), left-to-right IHTT calculated as latency difference at N170 peak between left and right hemisphere electrodes after RVF presentation (“B”, bottom panel).

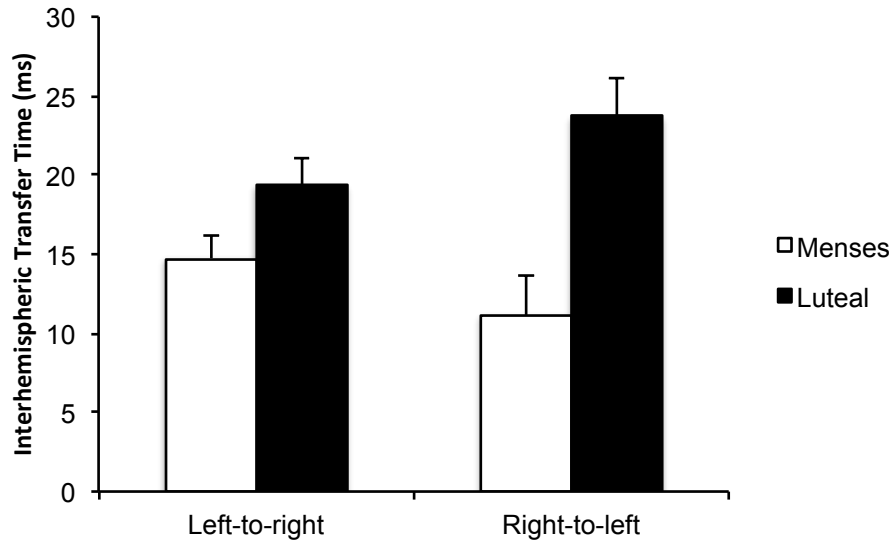


Figure 2. Interhemispheric transfer time (IHTT) in milliseconds and standard error means for left-to-right (left) and right-to-left transfer (right) during the menstrual phase (white bars) and luteal phase (black bars).

N170 latencies

Given that IHTT measures are based on both direct and indirect pathways, grand average N170 latencies were additionally subjected to 2 x 2 x 2 ANOVA with repeated measures with menstrual cycle (menstrual, luteal), hemisphere (left, right) and VHF (LVF, RVF) as within-subject factors (see Figure 3). The ANOVA revealed a significant hemisphere by VHF interaction ($F(1, 18) = 165.14, p < .001, \eta_p^2 = .90$), indicating that, as expected, the N170 latencies of the directly stimulated hemispheres were shorter than the latencies of the indirectly stimulated hemisphere. Specifically, for LVF stimulation, post hoc tests revealed shorter N170 latencies for the right hemisphere (direct pathway; $180 \text{ ms} \pm 11.16$) than the left hemisphere (indirect pathway; $197 \text{ ms} \pm 10.62$), $t(18)=9.99, p < .001$. After RVF stimulation, N170 latencies were shorter for the left hemisphere (direct pathway, $178 \text{ ms} \pm 11.00$) than the right hemisphere (indirect pathway; $197 \text{ ms} \pm 10.29$), $t(18) = 7.62, p < .001$. The interaction between menstrual cycle phase and hemisphere was also significant ($F(1, 18) = 9.74, p = .006, \eta_p^2 = .35$). Post hoc paired t-tests revealed longer latencies for the

right hemisphere ($190 \text{ ms} \pm 9.01$) than for the left ($187 \text{ ms} \pm 10.36$) during the menstrual phase, albeit this effect only approached significance, $t(18) = -1.84$, $p = .08$. During the luteal phase the N170 latencies for the left hemisphere ($189 \text{ ms} \pm 11.19$) did not differ from those of the right hemisphere ($187 \text{ ms} \pm 10.72$), $t(18) = 1.19$, $p = .25$. Finally, the three-way interaction was significant, $F(1, 18) = 7.53$, $p = .013$, $\eta_p^2 = .30$). Means and the standard error of the means of the N170 latencies are shown in Figure 3.

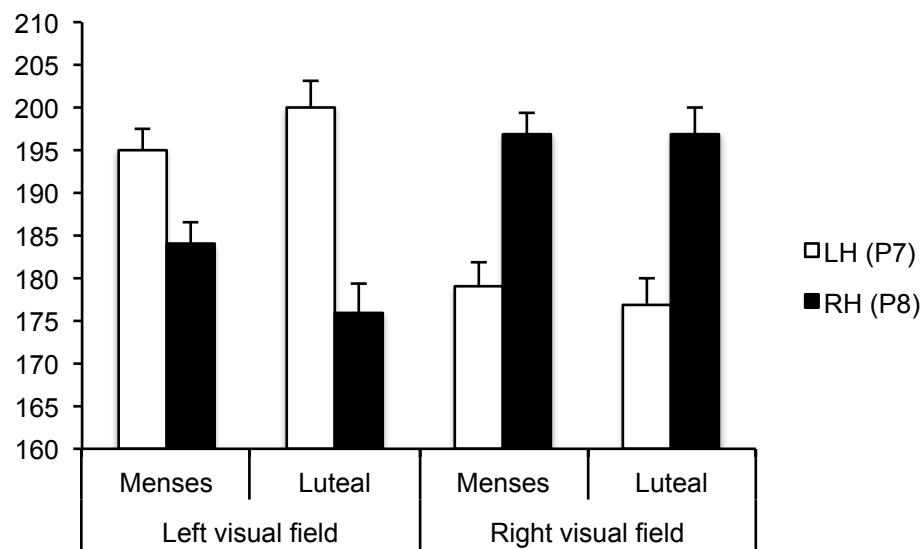


Figure 3. Grand average N170 latencies in milliseconds and standard error means of left parietal (P7, white bars) and right parietal leads (P8, black bars) after left visual half-field (LVF) and right visual half-field (RVF) stimulation during the menstrual (left bars) and luteal cycle phase (right bars).

To analyze the nature of the three-way interaction, two 2×2 ANOVAs were conducted separately for each VHF. For RVF, only the main effect of hemisphere was significant, $F(1, 18) = 58.03$, $p < .001$, $\eta_p^2 = .76$, indicating again shorter latencies of the directly than indirectly stimulated hemisphere. For LVF, the main effect of hemisphere, $F(1, 18) = 99.74$, $p < .001$, $\eta_p^2 = .85$, and the menstrual cycle by hemisphere interaction was significant, $F(1, 18) = 26.96$, $p < .001$, $\eta_p^2 = .60$. Post hoc paired t -tests revealed significantly

longer N170 latencies for the direct pathway (right hemisphere recordings after LVF stimulation) during the menstrual phase ($184 \text{ ms} \pm 10.49$) compared to those during the luteal phase ($176 \text{ ms} \pm 14.45$), $t(18) = 2.72$, $p = .014$). The N170 latencies of the indirect pathway (i.e., left hemisphere recordings after LVF stimulation) revealed the opposite pattern, that is, longer N170 latencies during the luteal phase ($200 \text{ ms} \pm 13.11$) compared to the menstrual phase ($195 \text{ ms} \pm 11.33$). This effect, however, only approached significance, $t(18) = 1.92$, $p = .07$).

Finally, we calculated two 2×2 ANOVAs with laterality (direct pathway: LVF/left hemisphere vs. RVF-right hemisphere; indirect pathway: LVF/right hemisphere vs. RVF/left hemisphere) and menstrual cycle as within-subject factors. The ANOVA for the direct pathways revealed a significant main effect of menstrual cycle, $F(1,18) = 6.18$, $p = .02$, $\eta_p^2 = .26$, indicating longer latencies during the menstrual than luteal phase. No other effect approached significance, all $F(1,18) < 1.82$, ns. For the indirect pathways, the interaction between laterality and menstrual cycle approached significance, $F(1,18) = 3.69$, $p = .07$, $\eta_p^2 = .17$, indicating a slowed left hemisphere latency after LVF stimulation (right-to-left transfer) in the luteal phase as compared to menses. This effect only approached significance ($p = .025$, alpha-adjusted) when tested with a one-tailed test, $t(18) = 1.92$, $p = .036$. In contrast, the right hemispheric response after RVF stimulation (left-to-right-transfer) was virtually identical across cycle phases, $t(18) = 0.00$, ns. No main effect approached significance, all $F(1,18) < 1.08$, ns.

Relationship between sex hormones and IHTT

Since the ANOVA results revealed significant cycle-related differences in directional IHTT and direct and indirect N170 latencies, we expected estradiol and/or progesterone levels to be significantly related to these measures. To test whether sex hormone levels are

related to slowed IHTTs (the increase in the indirect pathway, and the decrease in the direct pathway after LVF stimulation), we used stepwise multiple regressions. Left-to-right and right-to-left IHTTs, and direct and indirect N170 latencies after LVF and RVF stimulation were the criterions, and estradiol and progesterone levels were predictors. To rule out that mood contributed significantly to the observed effects (Compton & Mintzer, 2001), we also included mood scores (i.e. cheerfulness, seriousness and bad mood) as potential predictors in the regression analyses.

Since estradiol and progesterone levels within each phase showed only small inter-individual variation, and in order to cross-validate the regression models, we carried out the analyses twice, once for each session (i.e. session one and session two). This procedure has two advantages: (1) the inter-individual variability in estradiol and progesterone levels covers the whole range in hormone levels (from minimum to maximum); and (2) the regression model can be cross-validated by splitting the data according to session. Paired t-tests revealed no significant differences between session one and session two in estradiol and progesterone levels, mood scales, right-to-left and left-to-right IHTTs, and direct and indirect latencies after LVF and RVF stimulation, all $t(18) \leq 1.87$, n.s.

For session one, stepwise multiple regressions revealed a significant model for right-to-left IHTT when only estradiol was entered into the model, $F(1,18) = 6.33$, $p = .02$. The correlation between both variables was $r = .52$, $p = .02$, indicating that 27.1% of the variance in right-to-left IHTT can be explained by estradiol levels. The other predictors (i.e., progesterone levels and mood scores) were not significantly related to the dependent variable, all partial $r < .24$, n.s. There were no other significant effects for session one. Similarly, stepwise multiple regressions for session two did not reveal any significant correlations. Although estradiol levels were again positively related to right-to-left IHTT, this effect did not approach significance, $r = .32$, $p = .18$, thereby challenging the cross-validity of the

regression found in session one. Although the STCI might not be sensitive enough to detect cycle-related mood changes, multiple regressions did not revealed any relationships with mood scores.

Discussion

The present study has shown for the first time that IHTT, as assessed by EEG, fluctuates across the menstrual cycle. Specifically, we have shown that right-to-left IHTT is particularly affected, with significantly slower IHTT during the luteal phase, when levels of estradiol and progesterone (and their metabolites) are high, compared to IHTT in the menstrual phase, when sex hormone levels are significantly lower. The results also showed that it is the N170 latency in the right hemisphere after LVF stimulation (direct pathway) in particular that fluctuates across the menstrual cycle, with the longer N170 latencies occurring during the menstrual phase. Cycle-related differences of the left hemisphere N170 latencies after LVF stimulation only approached significance indicating a longer N170 latency of the indirect pathway during the luteal phase compared to the menstrual phase. In other words, although both direct and indirect N170 latencies in response to LVF stimulation fluctuate across the menstrual cycle, this effect was more robust for the direct pathway.

At first glance, dynamic changes in IHTT across the menstrual cycle are compatible with the hypothesis that sex hormone-mediated variations in FCA can be explained as hormone-modulated variations in the degree of interhemispheric coupling (Hausmann & Güntürkün, 2000). As discussed above, Hausmann and Güntürkün (2000) suggested that the increase in progesterone and/or estradiol (see Hausmann & Bayer, 2010, for details) results in interhemispheric decoupling during the luteal phase of the menstrual cycle. Furthermore, their model posits that the principal role of callosal communication (at least with respect to the emergence of FCAs) is the inhibition of one hemisphere by the other. However, although

there is evidence that IHTT is directly related to the structural integrity of the corpus callosum (e.g. Westerhausen et al., 2006; Whitford et al., 2011), the extent to which interhemispheric inhibition and IHTT share the same transcallosal mechanisms needs further consideration.

There is an ongoing debate as to whether interhemispheric crosstalk is predominantly inhibitory or excitatory, and there is good evidence for both (see Bloom & Hynd, 2005, for a review). One central conclusion by these authors is that the interhemispheric callosal projections may be both inhibitory and excitatory. The dominant interhemispheric influence might depend on the task and the specific interhemispheric process. Interhemispheric inhibition probably results from mainly glutamatergic transcallosal axons (e.g., Bloom, & Hynd, 2005; Conti & Manzoni, 1994). These excitatory axons terminate on GABAergic inhibitory interneurons (Toyama & Matsunami, 1976; Toyama, Tokashiki, & Matsunami, 1969) that induce a widespread inhibition in the contralateral hemisphere when activated (Clark & Zaidel, 1994; Kawaguchi, 1992). This increased inhibition of the subdominant hemisphere results in increased FCAs. In contrast, interhemispheric transfer and interhemispheric integration are assumed to rely primarily on excitatory transcallosal pathways (Van der Knaap & Van der Ham, 2011). Given that sex hormones are known to modulate both the glutamatergic and GABAergic system, high levels of estradiol, progesterone and their metabolites are assumed to modulate interhemispheric inhibition and FCAs (Hausmann & Güntürkün, 2000) as well as interhemispheric transfer and interhemispheric integration (Hausmann & Bayer, 2010), although the mechanisms of hormonal action may vary. Thus, on one hand, a hormone-related reduction of callosal communication can reduce the inhibition of neurons in one hemisphere by the dominant hemisphere for a particular task, resulting in an increase in bilateral activation, and reduced FCAs. Recent data from TMS (Hausmann et al., 2006) and fMRI (Weis et al., 2008; 2011)

strongly supports this view (see above). On the other hand, a hormone-related reduction of transcallosal excitation may also reduce the speed of interhemispheric transfer.

The current regression analyses revealed some support for a positive relationship between estradiol levels and right-to-left IHTT; the higher the level of estradiol, the slower the transfer time from right to left. As mentioned earlier, there is some evidence that estradiol affects interhemispheric processes (e.g., Hausmann, 2005; Holländer, Hausmann, Hamm, & Corballis, 2005; Weis et al., 2008). Although the neural mechanisms are not fully clear, estradiol is known to increase the glutamate response (Smith, Waterhouse, & Woodward, 1988). This should, however, potentiate glutamate-evoked excitation of transcallosal axons and accelerate IHTT, which is in contrast to the present findings. Alternatively, and in contrast to the general belief that IHTT depends mainly on excitatory transcallosal connections, it could be argued that high levels of estradiol might have non-specifically activated both hemispheres by increasing firing rates and increasing numbers of activated neurons (Dietrich et al., 2001). This would potentiate inhibitory processes between hemispheres (Weis et al., 2008), and consequently reduce the IHTT during the luteal phase. However, the estradiol effect found in the present study should be interpreted with caution because the relationship between estradiol and right-to-left IHTT failed cross-validation. Moreover, it should be noted again that IHTT is a composite score, calculated on the basis of both indirect and direct N170 latencies, and neither of them revealed a relationship with estradiol levels.

One explanation for the rather moderate relationship between estradiol and IHTT measures of the present study might be the relatively small sample size, and consequently low statistical power. It should be noted, however, that significant and robust estradiol-behaviour relationships have been shown with identical and even smaller samples (e.g. Hausmann, 2005; Weis et al., 2008). Also, it is possible that the relationship between

estradiol (and progesterone) levels and IHTTs and N170 latencies are not linear. Several previous studies found non-linear sex hormone/behaviour relationships (e.g. Gouchie & Kimura, 1991; Nyborg, 1988), suggesting an optimal hormone level for a specific neural/neuropsychological process. Finally, we cannot completely rule out the possibility that other sex hormones mediate the observed effects. Based on a non-linear relationship between testosterone levels and spatial cognitive abilities reported by Gouchie and Kimura (1991), the authors hypothesized that testosterone might have a “damping effect on the left hemisphere, perhaps through right-to-left callosal inhibition” (Gouchie & Kimura, 1991, p. 332). Although this hypothesis was not in the focus of the present study, it may explain sex differences in directional IHTTs. It is unlikely that this can account for the effects reported here however.

Previous EEG studies that looked at individual differences in IHTT found a shorter overall IHTT in women compared to men (Moes et al., 2007; Nowicka & Fersten, 2001). In addition, IHTTs for left-to-right and right-to-left directions were relatively symmetrical in women, whereas men revealed a directional asymmetry in IHTT. Specifically, men showed significantly shorter IHTT for right-to-left transfer compared to left-to-right, a finding that has repeatedly been found in right-handed men (e.g. Iwabuchi & Kirk, 2009). Nowicka and Tacikowski (2011) suggested that these findings might be interpreted in terms of the Galaburda hypothesis (Galaburda, Rosen, & Sherman, 1990), “stating that the more symmetrical a brain, the more transcallosal connection it has, and thus the faster the interhemispheric communication” (Nowicka & Tacikowski, 2011, p. 59). In line with these findings, right-handed women of the present study did not show significant directional asymmetries in IHTT *within* each cycle phase, although there was a trend towards a “male-like” faster right-to-left IHTT in the low hormone menstrual phase. The present study only revealed differences in right-to-left IHTTs *across* cycle phases (i.e. longer IHTT during the

luteal phase as compared to menses). There is still debate, however as to whether sex differences in the macro- and microanatomy of the corpus callosum exist and, if they do, what their functional relevance is (e.g. Bishop & Wahlsten, 1997; Westerhausen et al., 2011).

As mentioned above, IHTT is a composite measure of both direct and indirect pathways. Several previous studies have shown that the N170 latency over the hemisphere contralateral to the stimulated VHF (direct pathway) is unrelated to directional IHTT (e.g., Brown & Jeeves, 1993). This was, however, not the case in the present study. Here, cycle-related fluctuation of right-to-left IHTT was significantly affected by cycle-related changes in the N170 latency of the right hemisphere after LVF stimulation (direct pathway), whereas the cycle-related change in N170 latency of the left hemisphere after LVF stimulation (indirect pathway) only approached significance. These findings challenge our prediction that it is mainly the *interhemispheric* transfer that is hormonally affected and suggests that *intra*hemispheric communication times are also affected by sex hormones.

It is also of interest that cycle-related changes for both the direct and to some extent the indirect pathway occurred exclusively after LVF stimulation. This suggests that the right hemisphere is particularly sensitive to cycle-related changes. This is in line with previous studies suggesting that the right hemisphere is suppressed in normally cycling women during the luteal phase (e.g., Holländer et al., 2005; Sanders & Wenmoth, 1998; Rode et al., 1995) and in postmenopausal women using hormone therapy (Bayer & Hausmann, 2009a). In contrast, on the basis of their data from a visuospatial attention task, McCourt et al. (1997) concluded that both the left and right hemispheres might have been nonspecifically activated luteally, and a slight functional asymmetry favoring the right hemisphere might have been promoted. This conclusion is based on the well-known dominance of the right hemisphere in visuospatial attention, which includes a bilateral representation of the attentional spatial map in the right hemisphere and a strictly contralateral representation of the left hemisphere. The

former requires a richer commissural projection from the right to the left hemisphere for top-down attentional control of the response (Marzi, 2010). Nowicka and Tacikowski (2011) also suggested that the directional asymmetry in IHTT might reflect hemispheric specialization (i.e., FCAs). Interestingly, recent studies have shown that spatial attention (Hausmann, 2005) and attentional control (Hjelmervik et al., 2012) are modulated by estradiol, thereby modulating FCAs across the menstrual cycle. These findings might explain (a) the frequently reported faster right-to-left IHTT as compared to left-to-right IHTT, and (b) cycle-related changes in especially right hemisphere activation as reported in the present study.

It is important to note that three previous studies (Bayer & Hausmann, 2009b; Bayer et al., 2008; Schultheiss, Patalakh, & Rösch, 2012) have investigated sex- and sex hormone-related effects on IHTT before. However, these studies estimated IHTT on the basis of response time measures. Reaction time of the response made on the side contralateral to VHF stimulation (uncrossed condition) was subtracted from reaction time following ipsilateral stimulation (crossed condition). The results by Bayer and Hausmann (2008) showed that the crossed-uncrossed difference (CUD) in the Poffenberger task (Poffenberger, 1912), as an estimate of IHTT, did not fluctuate across the menstrual cycle and also did not differ between men and women (and postmenopausal women), regardless which cycle phase was taken into account. Similarly, the follow up study (Bayer & Hausmann, 2009b) did not find any modulating effects of hormone therapy on CUD in postmenopausal women. In contrast, a recent cross-sectional study (Schultheiss, Patalakh, & Rösch, 2012) found larger CUDs in women with high progesterone levels (indicative of the luteal phase) as compared to women with lower progesterone levels. This finding is similar to the present study, although the present study found some evidence for estradiol to play an important role. Unfortunately, Schultheiss and colleagues (2012) did not include estradiol levels (also elevated luteally) and

calculated CUDs on the basis of a more demanding decision task which complicates the comparison between studies.

It is also important to note that calculations of IHTT based on response time differences between crossed and uncrossed motor responses likely do not provide a reliable estimate of IHTT, as they measure processes other than the speed of interhemispheric transfer. In a recent comprehensive review, Nowicka and Tacikowski (2011) concluded that “the electrophysiological method of estimating IHTT, as performed in the present study, is definitely more reliable than behavioural methods” (Nowicka & Tacikowski, 2011, p. 54).

Although neither study mentioned above (Bayer & Hausmann, 2009b; Bayer et al., 2008) found effects of menstrual cycle or hormone therapy on CUD as an estimate of IHTT, they found significant effects on interhemispheric integration, as measured by the Banich-Belger task (see Banich & Belger, 1990, for details). This task measures the efficiency of integration of visual information across hemispheres by comparing bilateral and unilateral processing. It has been shown that across VHF integration, that allows for a division of labour between hemispheres, enhances performance when task complexity increases (across-field advantage; AFA) and impedes performance on less demanding tasks (Banich & Belger, 1990). Interestingly, Bayer et al. (2008) found a strong AFA for the more demanding (name-identity) task in normally cycling women during the luteal phase, which was identical to that of age-matched men and postmenopausal women. No AFA was found during the menstrual phase. Using the same approach, Bayer et al. (2009b) found that postmenopausal women using estrogen therapy or combined hormone therapy (estrogen plus gestagen) differed from postmenopausal controls in interhemispheric integration. More importantly here, postmenopausal women using hormone therapy differed from controls, especially in *intra*hemispheric processing (integration of visual information within VHF) which was improved across both tasks. In all three groups, the benefit of interhemispheric processing

(integration of visual information across VHF) equally increased in the more demanding task, indicating an efficient *interhemispheric* integration in postmenopausal women regardless of hormone therapy. In other words, although the absolute increase in the AFA, as a composite measure of across and within VHF integration, from the easier to the more demanding task was similar in all groups, women using hormone therapy showed a reduced relative efficiency of *interhemispheric* integration (i.e., strongly reduced AFA) as a result of an enhanced within-hemisphere performance (for review see Bayer & Hausmann, 2011). This finding also suggests that sex hormones can also affect *intra*hemispheric processing, which corresponds to the cycle-related effects found for the N170 latency in the right hemisphere after LVF stimulation (direct pathway) found in the present study.

In sum, the results of the present study show that cycle-related fluctuations in IHTT are based on N170 latencies of both indirect and direct neural pathways, albeit with the latter being particularly sensitive to sex hormonal changes. The findings occurred especially after LVF stimulation, suggesting that the right hemisphere plays a special role for the reported effects. The results of the present study are partly in line with the revised model of Hausmann and Güntürkün (2000) in that (a) hormone-related modulation of interhemispheric crosstalk is not restricted to the neuromodulatory properties of progesterone but also involves other hormones, such as estradiol, (b) cycle-related effects are not restricted to FCAs and interhemispheric inhibition but can be extended to other aspects of interhemispheric interaction, which probably rely more on excitatory transcallosal communication, and (c) sex-hormonal effects are not restricted to the modulation of processes between hemispheres but can also apply to cortical interactions within the hemispheres, particularly the right hemisphere. The results also suggest that levels of gonadal steroid hormones and menstrual state need to be controlled, if individual differences in IHTT and right hemisphere functioning are investigated, particularly those related to gender. The findings support the

idea that sex hormonal fluctuations across the menstrual cycle underlie dynamic changes in women's neural processes.

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